REMARKS

Preliminary to a scheduled interview, a draft of the attached declaration of Dr. Ulmer, unchanged as executed, and a draft proposal for claim amendments was provided to Examiner Wehbé for review. As a result of a telephone conversation with the Examiner following review of the materials, the interview was canceled. The Examiner requested that claim 1 be amended to recite administering the protein subsequent to the alphavirus vector construct. That change has been made herewith. The courtesy of the Examiner in considering the materials is gratefully acknowledged.

Amendments to the Claims

Claim 1 is amended to recite an alphavirus vector construct that directs the expression of the antigen portion of an antigen obtained from an intracellular pathogen. Support for this recitation is found, *inter alia*, at page 8, lines 26-29 of the specification. Claim 1 is also amended to recite administrating the protein subsequent to the alphavirus vector construct.

Rejection of Claims 1-5 and 26 Under 35 U.S.C. 103(a)

Claims 1-5 and 26 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 95/07994 ("Dubensky"), in view of Hu *et al.* AIDS Res. Hum. Retrovir., Vol. 7(7), 615-620 ("Hu").

Dubensky is cited as teaching replication competent and incompetent alphavirus vectors to express antigen and induce an antigen-specific response. Office Action at page

5. Dubensky is also cited as teaching priming and boosting with multiple administrations using the same vector. *Id.* Hu is cited as teaching boosting with protein. Office Action at pages 5. The Patent Office maintains at page 6 that "it would have been *prima facie* obvious to the skilled artisan to utilize the prime boost approach taught by Hu et al in the immunization method of Dubensky et al" and that "based on the state of the art in generating immune responses using replicating and non-replicating viruses, the skilled artisan would have had a reasonable expectation of success in generating an immune response." *Id.*

To advance prosecution, claim 1 is amended to recite administering a replication incompetent alphavirus vector construct comprising a polynucleotide encoding at least one immunogenic portion of an antigen followed by administering at least one protein which comprises at least one immunogenic portion of an antigen wherein said construct directs the expression of said antigen portion.

The Patent Office has not established a *prima facie* case of obviousness because, as set forth previously in the response filed May 12, 2008, there would have been no motivation to combine the teachings of Dubensky and Hu to arrive at the claimed subject matter. Hu employed only a single administration of the replicating vaccinia virus followed by a boost due to concerns about adverse interfering effects of anti-vector immunity. Page 618, col.1 ¶ 3. Because of this potential for interference, administering a protein boost makes sense for vaccinia viral vectors. Replication-defective alphaviral vectors, on the other hand, do not stimulate an interfering anti-vector immune response and thus can be administered repeatedly. Because there is no interfering anti-vector response, a skilled artisan would take advantage of repeated alphavirus administrations

rather than switching to a protein boost. Thus, because of this known difference in the viral vectors' properties, the skilled artisan would not be motivated to stop administering replication incompetent alphavirus and use a protein boost instead. A skilled artisan would thus have no reason to combine the teachings of Dubensky and Hu.

Even if, *arguendo*, a *prima facie* case of obviousness had been made, Applicants can rebut the *prima facie* case with unexpected results. Applicants enclose the declaration and CV of Dr. Jeffrey Ullmer. Dr Ullmer states that results from the present invention are significantly improved over Dubensky alone. ¶ 6. In support of his position, Dr Ullmer enclosed Exhibits 1 and 2, which present data obtained from practicing the claimed invention.

Exhibit 1 presents data from experiments testing immunogenicity and efficacy of non-replicating alphavirus replicon vectors in macaques, an art-recognized model for use in assessing protection from HIV infection. ¶ 3. The alphavirus prime-protein boost approach is compared to using alphavirus during both prime and boost stages. ¶ 4. Dr Ullmer states that "the best immunogenicity and protection were seen in animals primed with alphavirus and boosted with protein (slides 3 and 4) irrespective of the route of administration of alphavirus" *Id.* In contrast, using alphavirus during both the prime and boost phase "produced much lower levels of neutralizing antibodies (slide 3) and protection (group 4, slide 4) even though the replication incompetent alphaviral vector was able to express multiple copies of the protein antigen" *Id.*

The alphavirus prime-protein boost approach was also superior in rabbits: "Exhibit 2 shows that rabbits immunized using an alphavirus prime-protein boost

schedule responded with the higher titers of neutralizing antibodies against HIV SF-162, compared to immunization with protein alone or alphavirus alone." ¶ 5.

Dr Ullmer states that Hu's disclosure is limited to vaccinia, a replicating DNA virus, and "contains no description or suggestion that its protocol should be applied to a non-replicating RNA vector, such as an alphavirus replicating vector." ¶ 6. Dr Ullmer "concludes that Hu provides no basis for a skilled artisan to expect the robust responses obtained using the non-replicating alphavirus replicon vector prime and protein boost of this invention." *Id.*

A *prima facie* case of obviousness has not been made, and even if, *arguendo*, such a case was made, Dr. Ullmer's declaration rebuts the case by demonstrating the superior results obtained by practicing the claimed method. Claims 1-5 and 26 are not obvious.

Applicants therefore respectfully request withdrawal of the rejection.

Respectfully submitted,
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